EFFICACY OF INITIAL CHELATION WITH PENICILLAMINE FOLLOWED BY ZINC MONOTHERAPY IN SYMPTOMATIC WILSON'S DISEASE

A dissertation submitted in part fulfillment of the requirements for DM (Branch IV, Gastroenterology) examination of the Tamil Nadu Dr.M.GR. Medical University, Chennai to be held in August 2010

Certificate

This is to certify that this dissertation entitled 'Efficacy of initial chelation with penicillamine followed by zinc monotherapy in symptomatic Wilson's Disease' is a bonafide work done by Dr. Mehul Choksi in partial fulfillment of rules and regulations for DM (Branch IV-Gastroenterology) examination of the Tamil Nadu Dr. MGR Medical University, to be held in August 2010.

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DECLARATION

I, Dr Mehul Choksi hereby declare that this dissertation entitled 'Efficacy of initial chelation with penicillamine followed by zinc monotherapy in symptomatic Wilson's Disease' has been prepared by me under the direct supervision and guidance of Dr. C E Eapen, DM, Professor, Department of GI Scineces, Christian Medical College, Vellore being submitted to Dr M.G.R medical university in partial fulfillment of regulations for the award of DM degree in gastrointestinal sciences examination to be held in 2010.

This dissertation has not been submitted by me either in part or in full on any previous occasion to any university or institution for the award of any degree or diploma.

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INDEX

Introduction

Wilson's disease (WD) is an autosomal recessive disorder of copper metabolism which is caused by failure of biliary excretion of excess copper. The excess copper toxicity results in damage to the organs, primarily brain and/or liver [1]. This disorder is progressive and ultimately fatal if not recognized and treated.

There are a variety of agents used to remove copper from the body. In 1956, J M Walshe introduced D-penicillamine as a copper chelating agent that revolutionized the treatment of WD [2]. Although penicillamine is a good chelator of copper, it has a life threatening side effect profile and there is a high chance of neurological symptoms especially in neurological WD patients [3, 4, 5].

Zinc treatment for WD was reported in 1961 by Schouwink [6]. Zinc works by inducing intestinal metallothionein which preferentially binds to ingested copper within the duodenal enterocyte and copper is shed in the intestine during normal enterocyte turnover. Zinc also induces copper binding metallothionein in hepatocytes, thereby reducing the damaging effects of free copper [7]. Zinc has no major side effects other than gastric irritation especially with its sulfate salt.

Zinc monotherapy is presently recommended only for presymptomatic patients or those on maintenance therapy [8]. There are at present no recommendations for the use of zinc monotherapy in patients of WD with hepatic and /or neurological symptoms.

In our centre, the majority of WD patients cannot continue long term penicillamine due to its prohibitive cost. The aim of our study was to evaluate the efficacy of initial chelation with penicillamine followed by zinc monotherapy. We included symptomatic patients of

WD who were initiated on penicillamine but were unable to continue either due to financial constraints or the development of serious adverse effects of penicillamine.

Our study sets the platform for the search for an alternative safe, effective and affordable agent for the treatment of WD.

Review of Literature

Introduction:

Wilson's disease is a rare autosomal recessive genetic disorder of copper metabolism, which is characterised by hepatic and neurological disease. This disease was first described as a syndrome by Kinnier Wilson in 1912 as a "progressive lenticular degeneration", a familial lethal neurological disease accompanied by chronic liver disease leading to cirrhosis [9]. The disease affects between one in 30 000 to one in 100,000 individuals. Most symptoms appear in the second and third decades of life. In affected individuals, there is accumulation of excess copper in the liver caused by reduced excretion of copper in bile. The great danger is that Wilson's disease is progressive, can remain undiagnosed, and is fatal if not treated.

Molecular pathogenesis:

In 1993 the abnormal gene for WD was identified and pattern was found to be autosomal recessive [10,11,12]. The gene *ATB7B* on chromosome 13q14, encodes a transmembrane protein ATPase (ATP7B), which functions as a copper-dependent P-type ATPase. The ATP7B transporter has dual synthetic and excretory roles, functioning in the transport of copper into the trans-Golgi compartment, for incorporation into the plasma protein ceruloplasmin, and into the bile, for excretion of excess stores. Defective ATP7B function results in hepatic copper accumulation, which leads to the hepatic and neurological features of Wilson's disease.

Mutation of the protein ATP7B can interrupt its normal cellular processing. The most common ATP7B mutation found in patients of European origin is the histidine to glutamate substitution at aminoacid 1069 (H1069Q). In the hepatocytes of patients with Wilson's disease homozygous for H1069Q, ATP7B was mislocalised to the endoplasmic reticulum consistent with a failure of the mutant protein to undergo normal trafficking to its usual resident position in the trans-Golgi network. Dietary copper is absorbed in the stomach and duodenum and transported via the portal vein to the liver, which is the main organ responsible for copper homoeostasis. Copper is taken up into the hepatocyte via copper transporter 1 (CTR1) on the sinusoidal aspect of the hepatocyte. In the cytoplasm, glutathione and metallothionein proteins are important scavengers, protecting the cell from copper's toxic effects. A specific copper chaperone, ATOX1, delivers copper to the Wilson's disease protein, ATP7B, by copper-dependent protein-protein interaction. ATP7B brings about transport of copper into the trans-Golgi and holo-ceruloplasmin and, under conditions of copper loading, into vesicles for export of copper into bile [7].

The biliary excretion process includes another protein, COMMD1 (originally called MURR1), which interacts directly with ATP7B. Mutation of COMMD1 causes the copper toxicosis of Bedlington terriers—an autosomal recessive disorder that involves hepatic copper overload and deficient biliary copper excretion. However, sequencing and haplotype analysis reported no evidence to implicate the COMMD1 protein in copper-storage disorders of undefined aetiology in human beings [7].

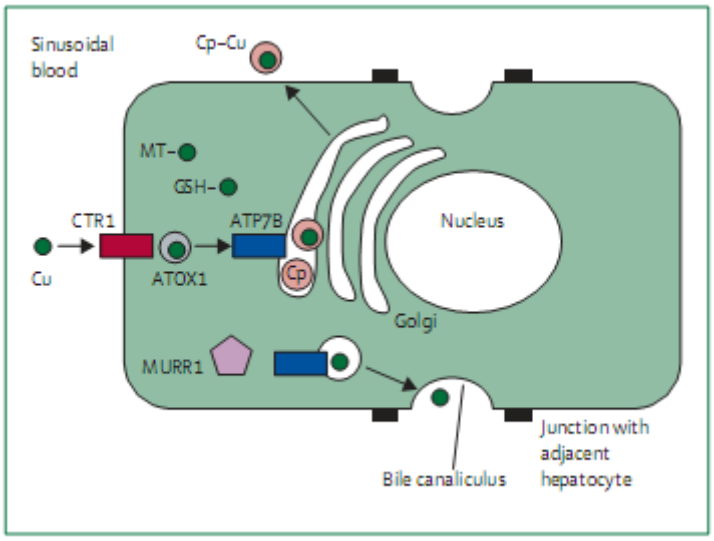


Figure 1: pathways of copper metabolism in the hepatocyte

Cu=copper. CTR1=copper transporter 1. MT=metallothioneins. GSH=glutathione. Cp=caeruloplasmin.

Mutation Analysis:

More than 260 reported mutations in the *ATP7B* gene have been detected in many different populations by single-strand conformation polymorphism analysis or by sequencing of each of the 21 exons [11,13,14]. These mutations are recorded in the WD Mutation Database [15]. High-throughput methods are making mutation analysis more feasible for this disease, as for many others. Mutation analysis can be carried out with approaches such as denaturing high-performance liquid chromatography [16] or by high-throughput sequencing of either selected or all exons of the gene.

The majority of mutations identified to date in *ATP7B* are missense mutations (57%). Small deletions and insertion (28%), nonsense (7%), and splice site (8%) mutations occur throughout the gene [15]. Various ethnic groups have different specific mutations. The

common histidine1069glutamine (His1069Gln) mutation [11] is present at least in the heterozygous state in 35% to 75% of Europeans with Wilson disease; the higher rate is relevant only for Eastern Europe [17]. Exon 8 of the gene is particularly rich in mutations in European populations; depending on the age of onset, at least one mutation can be identified in exon 8 in about 50% to 60% of patients [18]. The mutation arginine778leucine is common in Chinese populations [13]. Because no mutation is present in high frequency in Japanese and Mediterranean populations, mutation detection is more challenging in such populations. In some populations that have ethnic homogeneity or in which the spectrum of mutations is established, testing strategies can identify the mutations in more than 90% of patients, as in Sardinians, among whom Wilson disease occurs with a frequency of 1 in 7000 live births [19]. If the patient is clinically normal, has only slight signs of the disease, or has a late age of onset, that patient could actually be a heterozygote. However, up to now, heterozygotes have not been known to become clinically affected or to require treatment.

No individual biochemical test is reliable for the identification of patients. In some cases, even all combinations of tests prove inadequate for a diagnosis. The use of molecular tests in patients with any clinical symptoms of the disease may become routine in the near future and is already feasible in some populations.

Mutation analysis – Indian perspective:

The spectrum of ATP 7 B mutations in patients with WD, mostly from three southern Indian states and their family members were studied. The spectrum of ATP 7 B mutations were described including 11 novel mutations in Indian WD patients and were

documented lack of single dominant mutation. Identical WD phenotype among siblings in 6 of 8 families with > 1 child affected by WD suggests that factors other than ATP 7 B mutation influence WD phenotype [20].

In eastern India, WD patients from 109 unrelated families and their first-degree relatives comprising 400 individuals were enrolled to study the spectrum of ATP 7B mutations. In addition to previous reports, eight mutations including three novel (c.3412 + 1G > A, c.1771 G > A, c.3091 A > G) variants were identified. 17 mutations were identified in eastern India including five common mutations that account for 44% of patients. Comparative study on WD mutations between different regions of India suggests high genetic heterogeneity and the absence of a single or a limited number of common founder mutations. Genotype–phenotype correlation revealed that no particular phenotype could be assigned to a particular mutation and even same set of mutations in different patients showed different phenotypes [21].

In Northwest states of India there was absence of common mutations H1069Q, R778W and R778L mutations in WD patients. R778W and I1102T mutations were present in 36% of WD patients [22]. The copper ATPase activity in WD patients was significantly reduced (50%) than that of control individuals. No significant difference was observed in copper stimulated ATPase activity between homozygous (R778W/R778W, I1102T/I1102T) and compound heterozygous (R778W/unknown mutation, I1102T/unknown mutation) WD patients [22].

Pathology:

In the early stages before cirrhosis develops, histologic findings in the liver consist of steatosis, focal necrosis, glycogenated nuclei in hepatocytes, and sometimes apoptotic bodies [23]. As parenchymal damage progresses, possibly through repeated episodes of lobular necrosis, periportal fibrosis develops. Cirrhosis is usually macronodular but may be micronodular.

Early in the course of WD, hepatocellular copper is bound mainly to metallothionein and distributed diffusely in the cytoplasm of hepatocytes; therefore, results of histochemical stains for copper are negative. As the disease progresses, copper exceeds the capacity of metallothionein and is deposited in lysosomes. These lysosomal aggregates of copper can be detected by special staining techniques for copper or copper-binding protein (such as rubeanic acid or orcein). Copper is usually distributed throughout the hepatic lobule or nodule, but in the cirrhotic liver, some areas may have no stainable copper at all. If the clinical presentation mimics that of autoimmune hepatitis, liver biopsy specimens reveal classic histologic features of chronic hepatitis, such as interface hepatitis [24]. Inflammation may be severe. Results of Mallory staining for hyalin may be positive, and hepatocellular copper accumulation may be detected in upto 50% of biopsy specimens [25]. In patients who present with fulminant hepatic failure, liver biopsy confirms preexisting liver disease; cirrhosis may be present; and parenchymal copper is located mainly in Kupffer cells rather than in hepatocytes.

Changes in hepatocellular mitochondria, identified with electron microscopy, are an important feature in Wilson disease [24]. The mitochondria vary in size; the numbers of

dense bodies in mitochondria may be increased. The most striking change is dilatation of the tips of the mitochondrial cristae as a result of separation of the inner and outer membranes of the cristae, so that the intercristal space is widened to an irregular cystic shape. The crista resembles a tennis racquet if only the tip is dilated. Involvement of hepatocytes may not be uniform, so abnormalities may be found in some hepatocytes in some lobules and not in others. The mitochondrial changes are probably a consequence of oxidative damage from excessive liver copper.

Clinical Presentation:

The age at onset of symptoms generally ranges from 6 to about 40 years. WD with hepatic involvement has been identified in patients younger than 5 years and patients older than 60 years.

Hepatic presentation

Symptoms may be vague and nonspecific, such as fatigue, anorexia, and abdominal pain. Occasionally patients present with a self-limited clinical illness that resembles acute hepatitis, with malaise, anorexia, nausea, jaundice, elevated serum aminotransferases, and abnormal coagulation test results. Some patients have a history of self-limited jaundice, apparently caused by unexplained hemolysis.

Patients may present with severe, established chronic liver disease—hepatosplenomegaly, ascites, congestive splenomegaly, a low serum albumin level, and persistently abnormal

coagulation test results. Some patients have isolated splenomegaly without hepatomegaly. Many of these findings relate more to portal hypertension as a consequence of WD than to the metabolic disorder itself.

WD may manifest in children and young adults as clinical liver disease indistinguishable from autoimmune hepatitis [26]. As in autoimmune hepatitis, the onset may be acute. Fatigue, malaise, arthropathy, and rashes may occur; laboratory findings include elevated serum aminotransferase levels, a greatly increased serum immunoglobulin (Ig) G concentration, and detectable nonspecific autoantibodies such as antinuclear and anti–smooth muscle (anti-actin) antibodies. WD must be specifically ruled out because the treatment of the two diseases is entirely different. With appropriate treatment, the long-term outlook for patients with WD that manifests as autoimmune hepatitis appears to be favorable, even if cirrhosis is present.

WD may also manifest as fulminant hepatic failure, with severe coagulopathy and encephalopathy [27]. Acute intravascular hemolysis is usually present, and renal failure may develop. Unlike fulminant viral hepatitis, fulminant WD is usually characterized by disproportionately low serum aminotransferase levels (usually much less than 1500 U/L) at the onset of clinically apparent disease. The serum alkaline phosphatase level is in the normal range or even low for age, and the serum bilirubin level is often disproportionately high as a result of hemolysis [28]. A ratio of alkaline phosphatase concentration (IU/L) to bilirubin concentration (mg/dL) of less than two might be diagnostic of Wilsonian fulminant hepatitis [29,30]. Slit-lamp examination of the eyes may demonstrate Kayser-Fleischer rings. Urinary copper excretion is greatly elevated.

Affected patients do not show a good response to chelation treatment and require urgent liver transplantation; albumin dialysis and related techniques may serve as temporary procedures until liver transplantation can be performed [31].

Recurrent bouts of hemolysis may predispose to the development of gallstones. Children with unexplained cholelithiasis, particularly with small bilirubinate stones, should be tested for WD. Unlike other types of chronic liver disease, WD is rarely complicated by hepatocellular carcinoma.

In patients who have predominantly hepatic disease, evidence of subtle neurologic involvement often can be found. Mood disturbance (mainly depression, but sometimes impulsive or neurotic behavior), deterioration in school performance or handwriting, and clumsiness may be identified through careful questioning of the patient or his or her parents. A soft whispery voice (hypophonia) is another early feature of neurologic involvement.

Neurological and neuropsychiatric presentation:

Neurological and neuropsychiatric signs are the presenting features in 40–50% of patients with Wilson's disease [32]. The neurological abnormalities can be classified as: (a) an akinetic-rigid syndrome similar to Parkinson's disease, (b) pseudosclerosis dominated by tremor, (c) ataxia, and (d) a dystonic syndrome [33]. Subtle signs can appear before the characteristic neurological features, including changes in behaviour, deterioration of school work, or an inability to carry out activities that need good hand-eye coordination. Handwriting might deteriorate and micrographia—as in Parkinson's disease—could develop. Other common neurological findings include tremor, lack of motor coordination,

drooling, dysarthria, dystonia, and spasticity. Along with behavioural changes, other psychiatric manifestations include depression, anxiety, and frank psychosis [7].

Ocular signs

The classic Kayser-Fleischer ring is caused by copper deposition in Descemet's membrane of the cornea [34]. Copper is actually distributed throughout the cornea, but fluid streaming favors accumulation near the limbus, especially at the superior and inferior poles and, eventually, circumferentially around the iris. A careful slit-lamp examination is mandatory. Sunflower cataracts can also be seen [35]. Sunflower cataracts are brilliantly multicoloured and are visible only by slit-lamp examination. They do not impair vision. Both findings are reversible with medical therapy or after liver transplantation. Other less common findings include night blindness, exotropic strabismus, optic neuritis, and optic disc pallor.

Kayser-Fleischer rings may be absent in 15% to 50% of patients with exclusively hepatic involvement and in presymptomatic patients, whereas most patients with a neurologic or psychiatric presentation of WD have Kayser-Fleischer rings; only 5% do not. Kayser-Fleischer rings are not specific for WD. They may be found in patients with other types of chronic liver disease, usually with a prominent cholestatic component, such as primary biliary cirrhosis, primary sclerosing cholangitis, auto-immune hepatitis, and familial cholestatic syndromes. Kayser-Fleischer rings have also been reported in patients with nonhepatic diseases.

Involvement of the other organs [7]

WD can be accompanied by various extrahepatic disorders apart from neurologic disease. Episodes of hemolytic anemia can result from sudden release of copper into the blood. Renal disease, mainly Fanconi's syndrome, may be prominent. Findings include microscopic hematuria, aminoaciduria, phosphaturia, and defective acidification of the urine. Nephrolithiasis also has been reported. Arthritis, affecting mainly the large joints, may occur as a result of synovial copper accumulation. Other musculoskeletal problems are osteoporosis and osteochondritis dissecans. Vitamin D–resistant rickets may develop as a result of the renal damage. Copper deposition in the heart can lead to cardiomyopathy or cardiac arrhythmias. Sudden death in WD disease has been attributed to cardiac involvement but is rare. Copper deposition in skeletal muscle can cause rhabdomyolysis. Endocrine disorders can occur. Hypoparathyroidism has been attributed to copper deposition. Amenorrhea and testicular problems appear to result from WD itself, not from cirrhosis. Infertility or repeated spontaneous abortion may be a sign of WD. Pancreatitis, possibly resulting from copper deposition in the pancreas, may also occur.

Diagnosis of Wilson's disease

AASLD recommendations for diagnosis and screening for Wilson's disease [8]

Clinical features:

WD should be considered in any individual between the ages of 3 and 55 years (Wilson's disease has been diagnosed in patients in their seventies) with liver abnormalities of uncertain cause. Age alone should not be the basis for eliminating a diagnosis of WD.

WD must be excluded in any patient with unexplained liver disease along with neurological or neuropsychiatric disorder.

In a patient in whom WD is suspected, Kayser-Fleischer rings should be sought by slit-lamp examination by a skilled examiner. The absence of Kayser-Fleischer rings does not exclude the diagnosis of WD, even in patients with predominantly neurological disease.

Diagnostic testing:

An extremely low serum ceruloplasmin level (<50 mg/L or <5 mg/dL) should be taken as strong evidence for the diagnosis of WD. Modestly subnormal levels suggest further evaluation is necessary. Serum ceruloplasmin within the normal range does not exclude the diagnosis.

Basal 24-hour urinary excretion of copper should be obtained in all patients in whom the diagnosis of WD is being considered. The amount of copper excreted in the 24-hour

period is typically >100 mcg (1.6 micromol) in symptomatic patients, but finding >40 mcg (>0.6 micromol or >600 nmol) may indicate WD and requires further investigation.

Penicillamine challenge studies may be performed for the purpose of obtaining further evidence for the diagnosis of WD in symptomatic children if basal urinary copper excretion is <100 mcg/24 hours (1.6 micromol/24 hours). Values for the penicillamine challenge test of >1600 mcg copper/24 hours (>25 micromol/24 hours) following the administration of 500 mg of D-penicillamine at the beginning and again 12 hours later during the 24-hour urine collection are found in patients with WD. The predictive value of this test in adults is unknown.

Hepatic parenchymal copper content >250 mcg/g dry weight provides critical diagnostic information and should be obtained in cases where the diagnosis is not straightforward and in younger patients. In untreated patients, normal hepatic copper content (<40-50 mcg/g dry weight) almost always excludes a diagnosis of WD. Further diagnostic testing is indicated for patients with intermediate copper concentrations (70-250 mcg/g dry weight) especially if there is active liver disease or other symptoms of WD.

Neurologic evaluation and radiologic imaging of the brain, preferably by MR imaging, should be considered prior to treatment in all patients with neurologic WD and should be part of the evaluation of any patient presenting with neurological symptoms consistent with WD.

Mutation analysis by whole-gene sequencing is possible and should be performed on individuals in whom the diagnosis is difficult to establish by clinical and biochemical testing. Haplotype analysis or specific testing for known mutations can be used for family screening of first-degree relatives of patients with WD. A clinical geneticist may be required to interpret the results.

Diagnostic considerations in specific target populations:

Patients in the pediatric age bracket who present a clinical picture of autoimmune hepatitis should be investigated for WD.

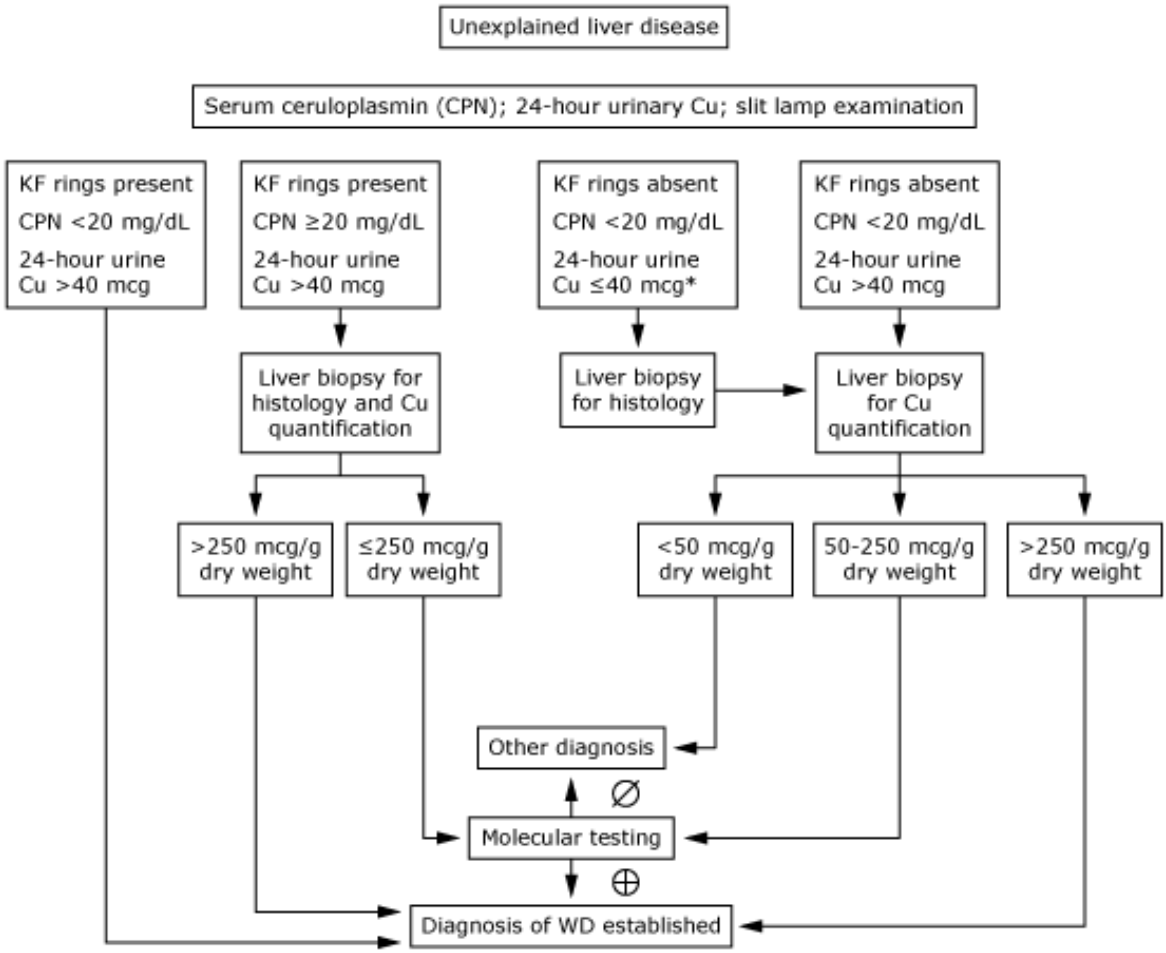
Adult patients with atypical autoimmune hepatitis or who respond poorly to standard corticosteroid therapy should also be investigated for WD.

WD should be considered in the differential diagnosis of patients presenting with nonalcoholic fatty liver disease or have pathologic findings of nonalcoholic steatohepatitis.

WD should be suspected in any patient presenting with acute hepatic failure with Coombs-negative intravascular hemolysis, modest elevations in serum aminotransferases, or low serum alkaline phosphatase and ratio of alkaline phosphatase to bilirubin of <2.

First-degree relatives of any patient newly diagnosed with WD must be screened for WD.

Approach to diagnosis of Wilson disease (WD) in a patient with unexplained liver disease



Molecular testing means confirming homozygosity for one mutation or defining two mutations constituting compound heterozygosity.

CPN: ceruloplasmin; KF: Kayser-Fleischer.

Criterion	Abnormality	Advantage	Disadvantage
Kayser–Fleischer corneal rings	Found on slit lamp examination	Easily assessed physical finding	Normal in 10–45% of patients, mainly the young
Serum ceruloplasmin	Less than 20 mg/l	Decreased in 73–95% of patients	Maybe normal, mainly with liver disease
24-hour copper excretion	More than 100 micrograms/ 24 hours	Increased in 85% of patients; useful in acute liver failure	Copper contamination and incomplete sample
Non-ceruloplasmin bound copper	More than 12 micrograms/dl	Increased when ceruloplasmin levels are normal	Not routinely reported
Liver copper quantitation	More than 250 micrograms/g dry weight	Increased in 90% or more of patients	Elevated in chronic cholestasis Sampling errors
Radiocopper scan	Lack of copper binding by ceruloplasmin	Differentiates homozygotes and heterozygotes	Blood samples over 48 hours

Predictive value of diagnostic criteria of Wilson’s disease

Treatment of Wilson's disease

History of treatment of WD:

In 1948, while investigating copper metabolism in demyelinating diseases, Mandelbrote et al.[36] observed an increase in the urinary excretion of copper in patients injected with 2,3 – dimercaptopropanol or BAL (British Anti – Lewisite). In 1951, Denny-Brown and Porter [37] and Cummings [38] introduced BAL as the first effective therapy for WD. Unfortunately the daily and indefinite intramuscular injection of BAL proved to be a painful and impractical form of therapy. Shortly thereafter J M Walshe (Cambridge, UK) introduced D-penicillamine (a dimethyl derivative of cysteine, which is found in the urine of patients on penicillamine) as an orally administered copper chelating agent. In 1956, Walshe introduced D-penicillamine into the pharmacopoeia and dramatically changed the profile of relentless progression of patients with untreated WD [2]. In 1969, Walshe introduced triethylene tetramine dihydrochloride or Trien as an alternative chelating agent to patients intolerant to D-penicillamine [39]. The use of zinc to decrease copper absorption may be attributed to Dick et al. who in 1954 reported that zinc supplementation in the diet of sheep led to a decrease in the liver copper content [40]. It was Schouwink [6] in 1961 who reported the use of zinc for WD, but zinc use got approval by FDA only in 1997 [41]. Recently a new drug ammonium tetrathiomolybdate has been used to treat neurological WD [42].

D-Penicillamine:

Penicillamine is cysteine, doubly substituted with methyl groups. A free sulphydryl group acts as the copper-chelator. D-penicillamine is rapidly absorbed from the gastrointestinal

tract with a double-peaked curve for intestinal absorption. Uptake may occur by an unusual mechanism: disulfide binding to the enterocyte membrane followed by pinocytosis. If D-penicillamine is taken with a meal, its absorption is decreased overall by about 50%. Total bioavailability is estimated at 40%-70%. Once absorbed, 80% of D-penicillamine circulates bound to plasma proteins; there is little free D-penicillamine in the plasma, because it forms inactive dimers or binds to cysteine. Greater than 80% of D-penicillamine excretion is via the kidneys. The excretion half-life of D-penicillamine is on the order of 1.7-7 hours, but there is considerable interindividual variation and D-penicillamine or its metabolites can be found in the urine months after the drug has been discontinued. Total bioavailability after oral administration is 40–70%. More than 80% of penicillamine excretion is in urine, with chelated copper. Thus, penicillamine enhances urinary copper excretion but can also lead to the sequestration of free intracellular copper [8]. Penicillamine can also induce metallothionein, a cysteine-rich protein that is an endogenous chelator of metals.

There are numerous studies that attest the efficacy of D-penicillamine as treatment of WD [43-49]. Worsening of neurologic symptoms has been reported in 10%-50% of those treated with D-penicillamine during the initial phase of treatment [50,51,52]. The hypothesis suggested for this phenomenon is that while penicillamine is mobilizing the very large store of hepatic copper, it temporarily further elevates the blood and brain levels of copper in the process [52].

D-Penicillamine use is associated with numerous side effects. Severe side effects requiring the drug to be discontinued occur in approximately 30% of patients [53]. Early sensitivity reactions marked by fever and cutaneous eruptions, lymphadenopathy, neutropenia or thrombocytopenia, and proteinuria may occur during the first 1-3 weeks. D-Penicillamine should be discontinued immediately if early sensitivity occurs; the availability of alternative medications makes a trial of prednisone cotreatment unnecessary. Late reactions include nephrotoxicity, usually heralded by proteinuria or the appearance of other cellular elements in the urine, for which discontinuation of D-penicillamine should be immediate. Other late reactions include a lupus-like syndrome marked by hematuria, proteinuria, positive antinuclear antibody and Goodpasture syndrome. Significant bone marrow toxicity includes severe thrombocytopenia or total aplasia. Dermatological toxicities reported include progeric changes in the skin and elastosis perforans serpingosa, and pemphigous or pemphigoid lesions, lichen planus, and aphthous stomatitis. Very late side effects include nephrotoxicity, severe allergic response upon restarting the drug after it has been discontinued, myasthenia gravis, polymyositis, loss of taste, immunoglobulin A depression, and serous retinitis. Hepatotoxicity has been reported. Hepatic siderosis has been reported in treated patients with reduced levels of serum ceruloplasmin and non–ceruloplasmin bound copper [8].

Tolerability of D-penicillamine may be enhanced by starting with incremental doses, 250-500 mg/day, increased by 250 mg increments every 4-7 days to a maximum of 1000-1500 mg/day in 2-4 divided dosages. Maintenance dose is usually 750-1000 mg/day administered in two divided doses. Dosing in the child is 20 mg/kg/day given in two or

three divided doses. D-Penicillamine is best administered 1 hour prior to or 2 hours after meals, because food inhibits its absorption. Serum ceruloplasmin may decrease after initiation of treatment. Serum ceruloplasmin may then either remain low or increase over the term of chronic treatment, the latter occurring in some patients with severe hepatic insufficiency as they recover synthetic function in response to treatment. In contrast, decrease in serum ceruloplasmin levels in patients treated chronically with penicillamine may be a sign of excessive copper depletion and often is associated with neutropenia, sideroblastic anemia, and hemosiderosis.

Adequacy of treatment is monitored by measuring 24-hour urinary copper excretion while on treatment. This is highest immediately after starting treatment and may exceed 1000 µg (16 µmol) per day at that time. With chronic (maintenance) treatment, urinary copper excretion should run in the vicinity of 200-500 µg (3-8 µmol) per day on treatment. In addition, estimate of non–ceruloplasmin bound copper shows normalization of the non–ceruloplasmin bound copper concentration with effective treatment. Values of urine copper excretion below 200 µg/day (3.2 µmol/day) may indicate either nonadherence to therapy or overtreatment and excess copper removal. In those with nonadherence to therapy, non–ceruloplasmin bound copper is elevated (>15 µg /dL or >150 µg /L) while with over treatment, values are very low (<5 µg /dL or <50 µg /L) [8].

Trientine:

Trientine (triethylene tetramine dihydrochloride or 2,2,2-tetramine, also known by its official short name trien) is one of a family of chelators with a polyamine-like structure

chemically distinct from penicillamine. It lacks sulfhydryl groups and copper is chelated by forming a stable complex with the four constituent nitrogens in a planar ring. Trientine was introduced in 1969 as an alternative to penicillamine. It is poorly absorbed fromthe gastrointestinal tract.

The amounts of urinary copper, zinc and iron increase in parallel with the amount of trientine excreted in the urine [54]. Like penicillamine, trientine promotes copper excretion by the kidneys. Trientine is effective treatment for WD and is indicated especially in patients who are intolerant of penicillamine or have clinical features indicating potential intolerance (history of renal disease of any sort, congestive splenomegaly causing severe thrombocytopenia, autoimmune tendency) [55]. Neurological worsening after beginning treatment with trientine has been reported but appears much less common than with penicillamine. Trientine has also been shown to be effective initial therapy for patients, even with decompensated liver disease at the outset [56]. Trientine has few side effects. No hypersensitivity reactions have been reported although a fixed cutaneous drug reaction was observed in one patient. Pancytopenia has rarely been reported. Trientine also chelates iron, and coadministration of trientine and iron should be avoided because the complex with iron is toxic. A reversible sideroblastic anemia may be a consequence of overtreatment and resultant copper deficiency. Lupus-like reactions have also been reported in some WD patients treated with trientine.

Typical dosages are 750-1500 mg/day in two or three divided doses, with 750 or 1000 mg used for maintenance therapy. In children, the weight-based dose is not established, but

the dose generally used is 20 mg/kg/day rounded off to the nearest 250 mg, given in two or three divided doses. Trientine should be administered 1 hour before or 2 hours after meals. Adequacy of treatment is monitored by measuring 24-hour urinary copper excretion while on treatment. This should run in the vicinity of 200-500 µg (3-8 µmoles) per

day on maintenance treatment but may be higher when treatment is first started. Additionally, estimate of non–ceruloplasmin bound copper may show normalization of the non–ceruloplasmin bound copper concentration with effective treatment. Values of urine copper excretion below 200 µg/day

(3.2 µmol/day) may indicate either nonadherence to therapy or overtreatment and excess copper removal. In those with nonadherence to therapy, non–ceruloplasmin bound copper is elevated (>15 µg/dL or >150 µg/L), whereas with overtreatment, values are very low (<5 µg/dL or <50 µg/L) [8].

Zinc:

The mechanism of action of zinc is different from that of penicillamine and trientine. Zinc intereferes with the uptake of copper from the gastrointestinal tract. Oral ingestion of zinc induces in intestinal cells the synthesis of a protein, metallothionein, a cysteine-rich protein that is an endogenous chelator of metals [7,57]. Metallothionein has greater affinity for copper than for zinc and thus preferentially binds copper present in the enterocyte and inhibits its entry into the portal circulation. Once bound, the copper is not absorbed but is lost into the fecal contents as enterocytes are shed in normal turnover. Because copper also enters the gastrointestinal tract from saliva and gastric secretions,

zinc treatment can generate a negative balance for copper and thereby remove stored copper [58]. Zinc may also act by inducing levels of hepatocellular metallothionein [59].

Zinc has very few side effects. Gastric irritation seen in 5 to 10% of patients and may be dependent on the salt employed [41]. Zinc sulfate has more gastric irritant effects than zinc acetate. This can be easily ameliorated by taking the first dose of the day mid-morning, rather than before breakfast [42]. Other findings noted with zinc therapy include possible immunosuppressant effects and reduced leucocyte chemotaxis but one study found no adverse effect on lymphocyte function with chronic use [60]. Elevations of amylase and lipase that tend to occur during the first year of zinc therapy are attributed to inductions of these enzymes by zinc and therefore a greater release in the plasma [60]. Studies have noted that zinc has an effect on reducing high density lipoprotein cholesterol, the type of cholesterol associated with reducing the risk of coronary heart disease [61,62]. Brewer et al.; have studied cholesterol metabolism in zinc treated patients with Wilson's disease and found no harmful effects [41,63].

Brewer et al.; have recommended elemental zinc dosages as follows: 25 mg x 2 until age 6, 25 mg x 3 until age 16 or until reaching a weight of 125 pounds, and then the regular dose of 50 mg x 3 [41]. This study also states that the above doses provide a margin of safety. If a patient forgets his or her medication over a few days such as a weekend, the metallothionein in the intestinal tract will stay induced (the half-life of deinduction is 11 days) and the patient will continue to be protected [41]. Adequacy of treatment with zinc is judged by clinical and biochemical improvement and by measuring 24-hour

urinary excretion of copper, which should be less than 75µg (1.2 µmol) per 24 hours on stable treatment. Additionally, estimate of non–ceruloplasmin bound copper shows normalization of the non–ceruloplasmin bound copper concentration with effective treatment. Urinary excretion of zinc may be measured from time to time to check compliance [8]. Patients on zinc also have a risk of being over treated. This would be manifest with a urine copper level that drops below 35 µg/24 hours (normal 20 to 50 µg) and later by hypochromic microcytic anemia and leucopenia. It is suggested to lower the dose of zinc [41].

Ammonium Tetrathiomolybdate (TM):

TM is a very strong decoppering agent which works by two mechanisms: interfering with intestinal uptake of copper (if administered with meals) and binding copper from plasma (when taken between meals). At low doses, TM removes copper from metallothionein, but at higher doses it forms an insoluble copper complex, which is deposited in the liver [8,42]. TM has been used in Wilson's disease for the initial treatment of the neurologically presenting patient and is currently being investigated for the initial treatment of the hepatic presentation as well. The dose is 120 mg/day, 20 mg three times/day with meals, and 60 mg at bedtime away from food, given for eight weeks, concomitant with zinc therapy. The measure of efficacy has been the rate of neurological deterioration, which has been less than 5% with TM (compared to 50% for penicillamine and a little less than 20% for trientine) [64].

TM has a good safely profile. There is a 10–15% incidence of overtreatment anemia/leukopenia, responsive to lowering the dose. There is also a 10–15% incidence of a mild further increase in transaminase enzymes, probably due to TM's ability to shift copper out of hepatic metallothionein pools. This, too, is quickly responsive to lowering the dose. Currently a study is underway to see if a lower dose given longer will preserve efficacy and reduce side effects [64].

Role of Diet in treatment of Wilson's disease [8]:

Foods with very high concentrations of copper (shellfish, nuts, chocolate, mushrooms, and organ meats) generally should be avoided, at least in the first year of treatment. Diets deficient in copper may delay the onset of the disease and control disease progression, but dietary management is not recommended as sole therapy. Well water or water brought into the house hold through copper pipes should be checked for copper content, but in general, municipal water supplies do not have to be checked. A water purifying system may be advisable if the copper content of the water is high. For those with copper pipes, it is important to flush the system of stagnant water before using water for cooking or consumption. Copper containers or cookware should not be used to store or prepare foods or drinks.

Treatment of Wilson's disease in Specific Clinical Situations

Asymptomatic patients:

Presymptomatic patients are those that are diagnosed before becoming clinically ill. Usually these will be siblings of an affected patient who are diagnosed as a result of family screening. Occasionally a presymptomatic patient will be dentified when routine ophthalmologic examination reveals Kayser-Fleischer rings, or when routine serum biochemistries reveal elevated serum transaminase enzymes**.** These patients may be viewed as equivalent to symptomatic patients who have received initial therapy and are in the maintenance phase of treatment. They can be treated either with chelating agent D-penicillamine/ trientine monotherapy or with zinc monotherapy [3,42,65,66,67,68].

Initial therapy – neurologic patients:

A major problem exists with the initial therapy of neurologic patients in that all of the drugs currently available commercially have defects in treating these patients. Penicillamine has a high rate (10 - 50%) of causing neurologic worsening, probably by mobilizing hepatic copper and temporarily further elevating brain copper [50,51,52]. About half of the patients who worsen never recover to their prepenicillamine baseline. Trientine, which is a chelator like penicillamine, appears to have about a 20% risk of causing neurologic worsening [69]. It is suggested to start at a lower dose of chelator and gradually hike to the optimal dose to prevent neurological worsening. Linn et al.; have reported a good clinical outcome of patients with neurologic WD treated with exclusive zinc therapy with a median follow up of 14 years [70].

Initial therapy – Hepatic patients:

If the patient simply has transaminase elevations, or cirrhosis and transaminase elevations, but no evidence of hepatic decompensation in terms of low albumin, elevated bilirubin, and prolonged prothrombin time, the patient may be treated as a maintenance phase patient with zinc or trientine [42].

Patients who present with decompensated chronic liver disease, typically with hypoalbuminemia, prominent coagulopathy, ascites, but no encephalopathy, have recently been treated with a chelator, either D-penicillamine or trientine plus zinc [8]. There are at present no recommendations to start zinc therapy in symptomatic and decompensated liver disease patients. The study by Linn et al.; in which exclusive zinc therapy for WD patients, concluded a less favourable outcome for patients with hepatic presentation. Two of the twelve patients with compensated cirrhosis deteriorated on follow up needing for liver transplantation [70].

Patients with acute liver failure due to WD require liver transplantation which is life saving [71]. To help determine which patients with acute hepatic presentations will not survive without liver transplantation, Nazer et al.; developed a prognostic score whose components include serum bilirubin, serum aspartate aminotransferse, and prolongation of prothrombin time [72]. The study implies that patients with scores of 6 or below were likely to survive on penicillamine therapy, while those with scores of 7 or above were not unless transplanted [72].

Laboratory measurement	Normal value	Score (in points)				
		0	1	2	3	4
Serum bilirubin	0.2–1.2 mg/dl	<5.8	5.8–8.8	8.8–11.7	11.7–17.5	>17.5
Serum aspartate transferase (AST)	10–35 IU/L	<100	100–150	151–200	201–300	>300
Prolongation of prothrombin time (seconds)	–	<4	4–8	9–12	13–20	>20

Nazer score [72]

Maintenance therapy:

As per the AASLD practice guidelines, after adequate treatment with a chelator, stable patients may be continued on a lower dosage of the chelating agent or shifted to treatment with zinc [8]. The advantages of long-term treatment with zinc include that it is more selective for removing copper than penicillamine or trientine and is associated with few side effects. The study by Brewer et al on 141 patients, it was concluded that zinc is effective as the sole therapy in long term treatment maintenance treatment of Wilson's disease [73]. The prospective study of Czlonkowska et al.; compared the clinical outcome in patients treated with penicillamine or zinc. They concluded that both drugs were equally effective in the long term of treatment of WD. The tolerance profile was in favour of zinc sulfate [49].

Pregnancy:

In pregnant women, treatment must be maintained throughout the course of pregnancy for all patients with WD. Experience to date indicates the chelating agents (both penicillamine and trientine) and zinc salts have been associated with satisfactory outcomes for the mother and fetus [74,75,76,77]. Birth defects are rare. The dosage of zinc salts is maintained throughout without change; however, dosages of chelating agents should be reduced to the minimum necessary during pregnancy, especially for the last trimester to promote better wound healing if cesarean section is performed. Such a dose reduction might be on the order of 25%-50% of the pre pregnancy dose. Patients should be monitored frequently during pregnancy. Women taking D-penicillamine should not breast-feed because the drug is excreted into breast milk and might harm the infant. Little is known about the safety of trine tine and zinc in breast milk [8].

Aim

- To study the efficacy of initial chelation with penicillamine followed by zinc monotherapy in symptomatic Wilson's disease.

Material and Methods

We performed an open retrospective and prospective observational cohort study to evaluate the efficacy, safety and outcomes of symptomatic WD patients treated with initial penicillamine followed by zinc monotherapy. The study was approved by the Institutional Review Board and Ethics Committee. Written consent was taken from all patients included in the study. The study was conducted over a period of 2 years from October 2007 to October 2009 in the Department of Gastrointestinal Sciences at CMC, Vellore.

Inclusion Criteria:

- Symptomatic WD (Hepatic +/- Neuropsychiatric) on treatment with penicillamine

Hepatic manifestations included jaundice, ascites, gastrointestinal bleed, encephalopathy, abdominal pain or spontaneous bacterial peritonitis.

Exclusion criteria:

- Diagnosis other than WD / doubtful WD
- Atypical copper deposition disease
- Presymptomatic WD
- Any other coexisting liver disease
- WD treated with any other regime

Sample Size:

This was an observational cohort study. We estimated that during the study duration about 20 patients would be on follow up with the aforementioned treatment regime in our unit.

Methodology:

The database of patients with the diagnosis of WD was generated using medical records and a prior genetic base study. Pharmacy records of these patients were retrieved online. The patients who were initially on D-penicillamine and changed to zinc sulphate later on were screened and all those who fulfilled all the inclusion criteria and had none of the exclusion criteria were recruited and formed the study cohort.

The diagnosis of Wilson's disease was made based on clinical presentation of liver disease and confirmatory tests which included serum Ceruloplasmin values, 24 hours urinary copper excretion with or without presence of Kay Fleischer ring. Percutaneous or transjugular liver biopsy for assessing the histology and dry weight of copper and ATB 7B gene mutation analysis were done as and when clinically indicated.

Those patients who were on penicillamine at the start of the study changed over to zinc because of financial constraints or adverse effects. The change over from penicillamine to zinc was gradual, by tapering and stopping penicillamine over a few months in those patients who attained clinical stability with initial chelation with penicillamine but had financial constraints. In contrast in those patients who had adverse effects to

penicillamine, the drug was abruptly stopped and changed to zinc. The dose of penicillamine used in the study cohort varied from 250 mg bid to 250 mg qid. The dose of zinc sulphate varied from 140 mg bid to 140 mg tid. The study cohort was followed up periodically on outpatient basis and as inpatients during hospital admissions. The patients were seen by the primary investigator on each follow up visit and clinical worsening or improvement was recorded. In addition at each of these visits, compliance and adverse effects to zinc sulphate were noted. Compliance was assessed by enquiring the patient or their parents about regular drug intake. The patients had periodic monitoring of hemoglobin, total and differential white cell counts, platelet count, liver function tests and prothrombin time, although all tests were not ordered at each visit by the treating physician. Urinary copper and ceruloplasmin values on follow up were also noted, if available.

The results were analyzed based on the clinical and laboratory parameters from entry into study and till October 2009. The data entry and analysis was done using Microsoft Excel and Graphpad Instat 3. ANOVA was the statistical test used for comparing the means of variables at baseline, on penicillamine and on zinc therapy.

The laboratory parameters (hemoglobin, total and differential white cell counts, platelet count, liver function tests, prothrombin time, 24 hour urinary copper excretion) at presentation, on penicillamine and on zinc therapy were compared. We calculated the Model for End Stage Liver Disease (MELD), Nazer score and New Wilson Index for predicting Mortality at presentation, on penicillamine and on zinc subject to availability

of laboratory parameters at each visit. The outcome parameters studied were morbidity and mortality, complications of liver disease and changes in laboratory parameters on treatment with each drug. The side effect profile was also studied.

Results

Demographic profile:

202 patients were screened out of which 28 who fulfilled all the inclusion criteria and had none of the exclusion criteria were recruited into the study. The study included 28 patients, males (n=18) and females (n=10). The mean age of subjects was 17.5 ± 6.19 years.

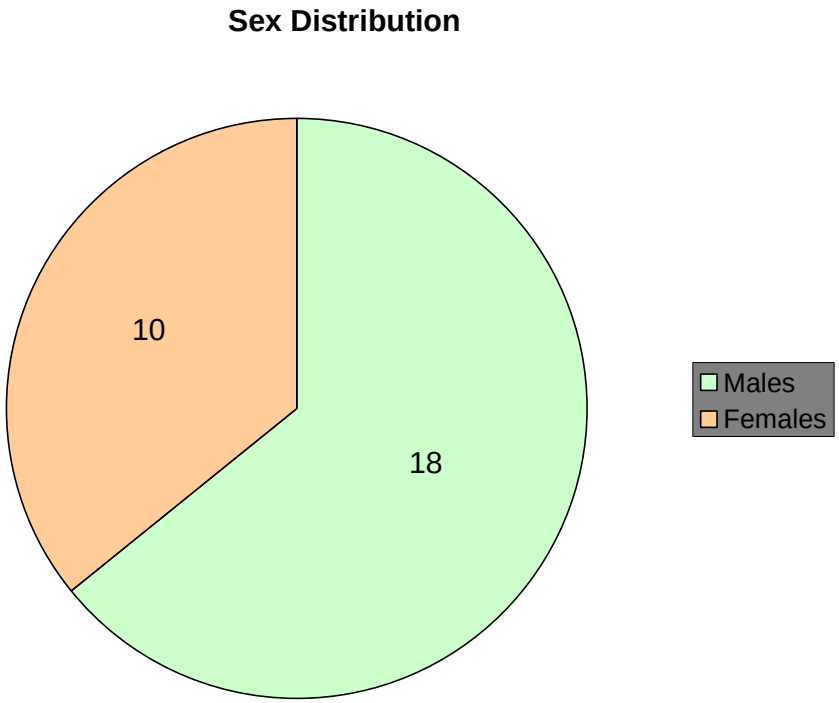


Figure 1 – Figure to show the sex distrubution of patients

Twenty four patients had pure hepatic manifestations. Hepatic and neurological symptoms were present in two patients. 2 others had psychiatric complaints in addition.

Twenty four patients presented with some form of hepatic decompensation, whereas the remaining had abdominal pain as the chief complaint. The patients had the following hepatic symptoms: ascites (n=16), jaundice (n=14), abdominal pain (n=8), gastrointestinal bleeding (n=4) and encephalopathy (n=2).

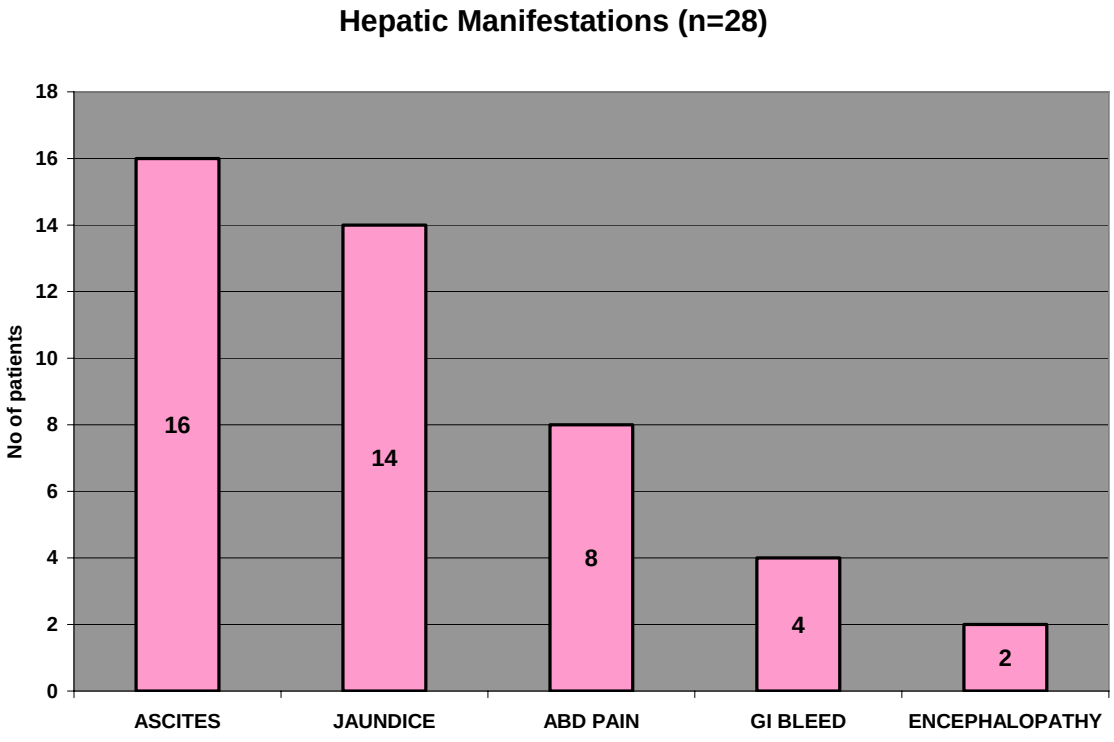


Figure 2 – Figure to show the distribution of hepatic manifestations

The neurological presenting features were drooling of saliva (n=2), writing difficulty (n=1), rigidity (n=1) and abnormal movements (n=1). Psychiatric manifestations included poor scholastic performance and cognitive decline (n=1) and behavioral changes (n=1).

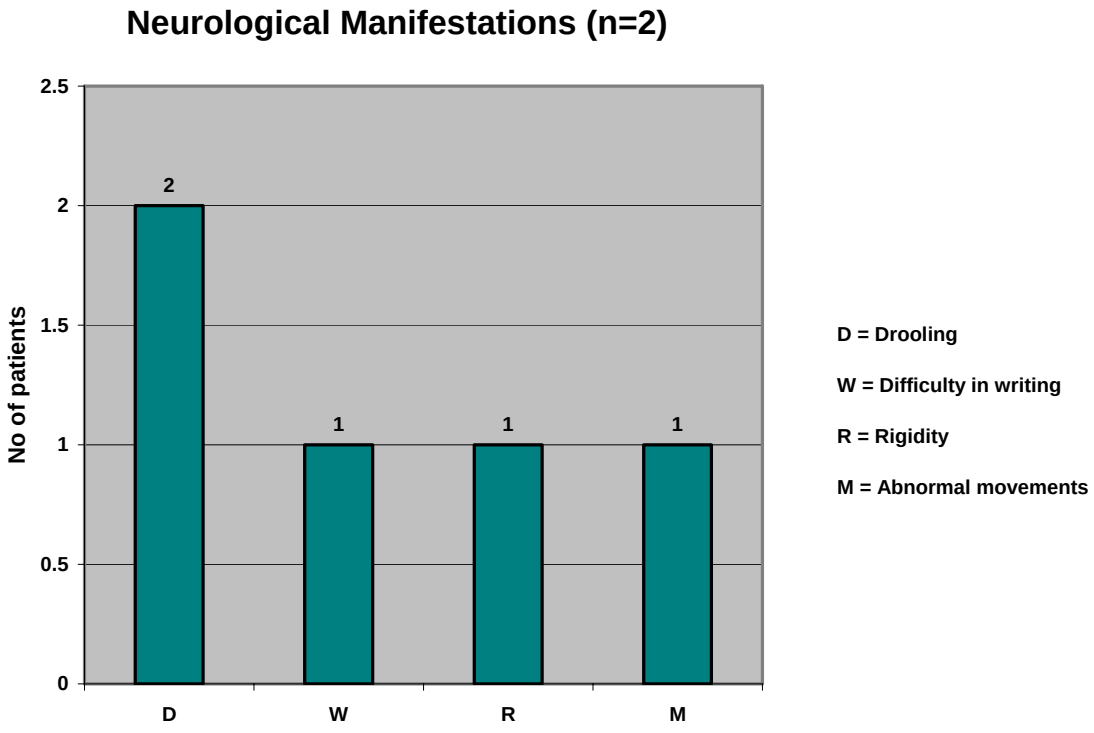


Figure 3 - Figure to show the distribution of neurological manifestations

Psychiatric manifestations included poor scholastic performance and cognitive decline (n=1) and behavioral changes (n=1).

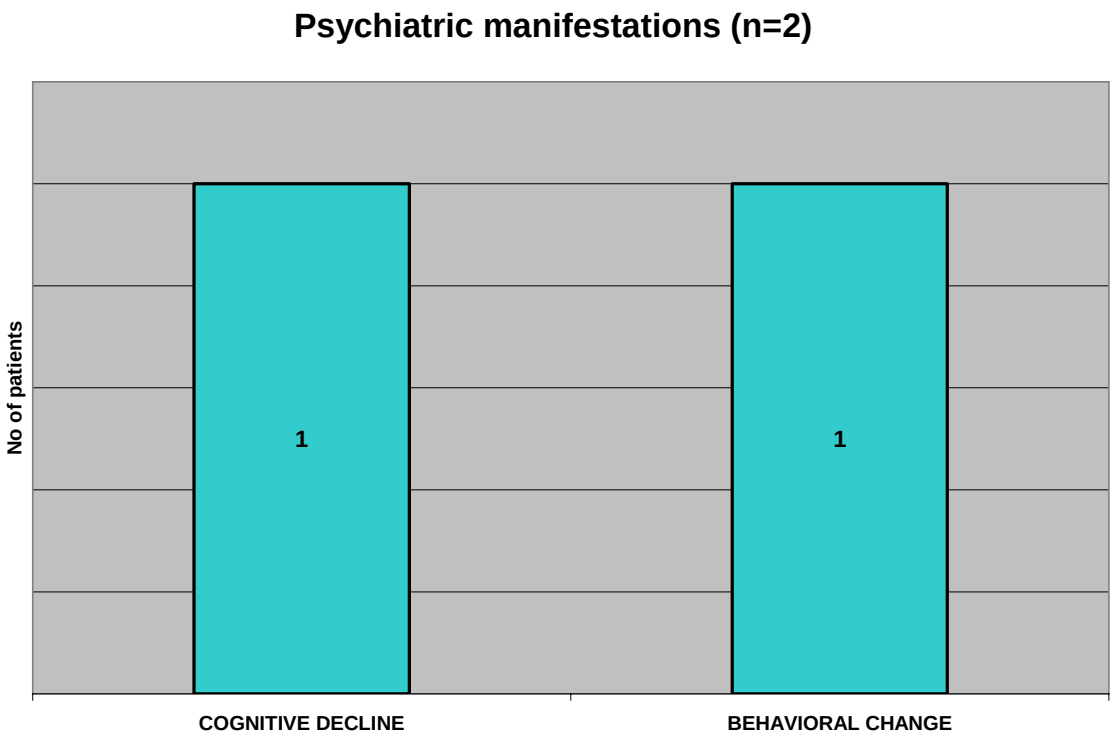


Figure 4 - Figure to show the distribution of psychiatric manifestations

Duration of treatment:

The mean duration of penicillamine therapy was 123.92 weeks (SD: 94.18; range: 2-320 weeks). The mean duration of zinc therapy was 175.92 weeks (SD: 122.82; range: 21 to 352 weeks). The mean duration of therapy was significantly longer for zinc compared to penicillamine (p=0.03).

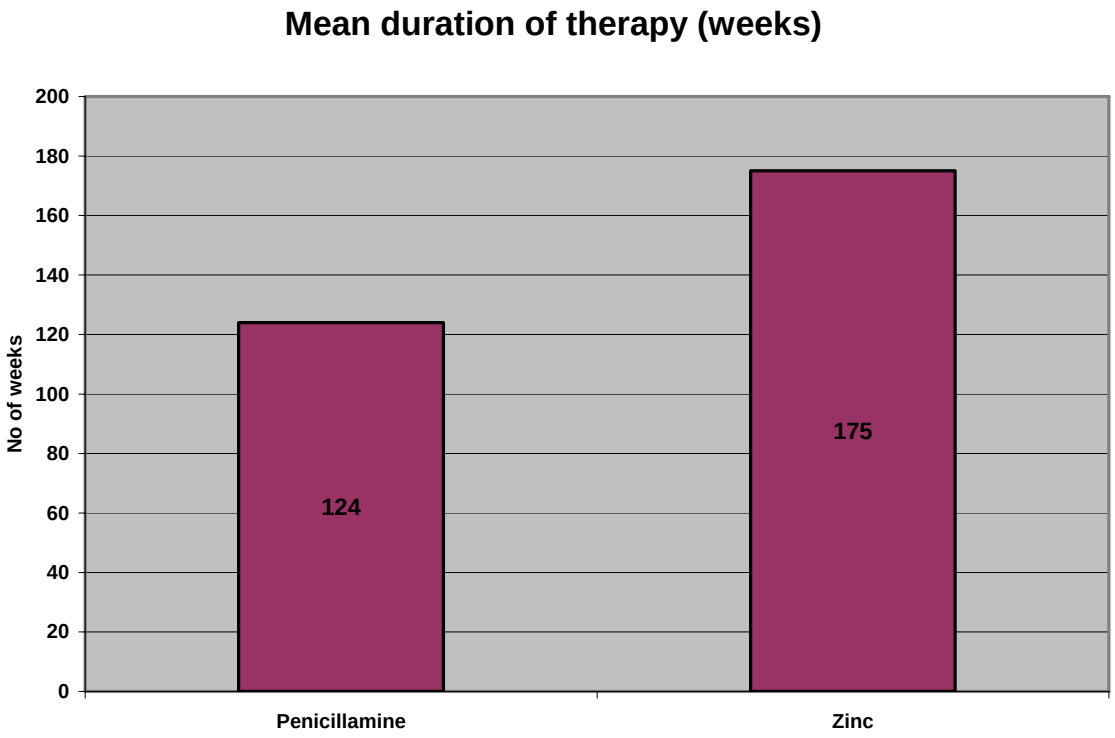


Figure 5 - Figure to show mean duration of penicillamine and zinc therapy

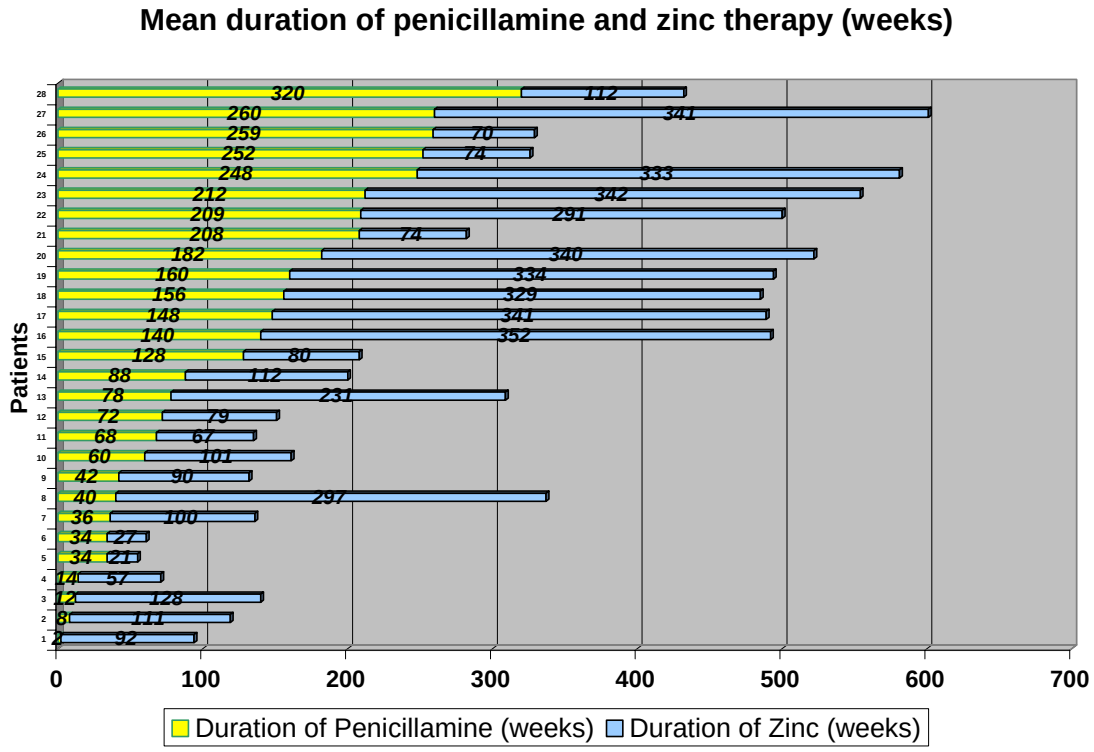


Figure 6 - Figure to show duration of penicillamine and zinc therapy in individual subjects

Statistical analysis and results:

The Analysis of Variance (ANOVA) test was used to look for variation among means of variables at baseline, on penicillamine and zinc monotherapy.

The mean serum bilirubin values at presentation, on penicillamine and on zinc were 3.88 mg%, 1.73 mg% and 1.56 mg% respectively. The variation among the aforementioned mean values of bilirubin was not significant (p=0.0778). So also, no statistically significant difference was obtained when the following means of serum bilirubin were compared a) at presentation vs penicillamine (p >0.05) b) at presentation vs zinc monotherapy (p >0.05) c) penicillamine vs zinc monotherapy (p>0.05).

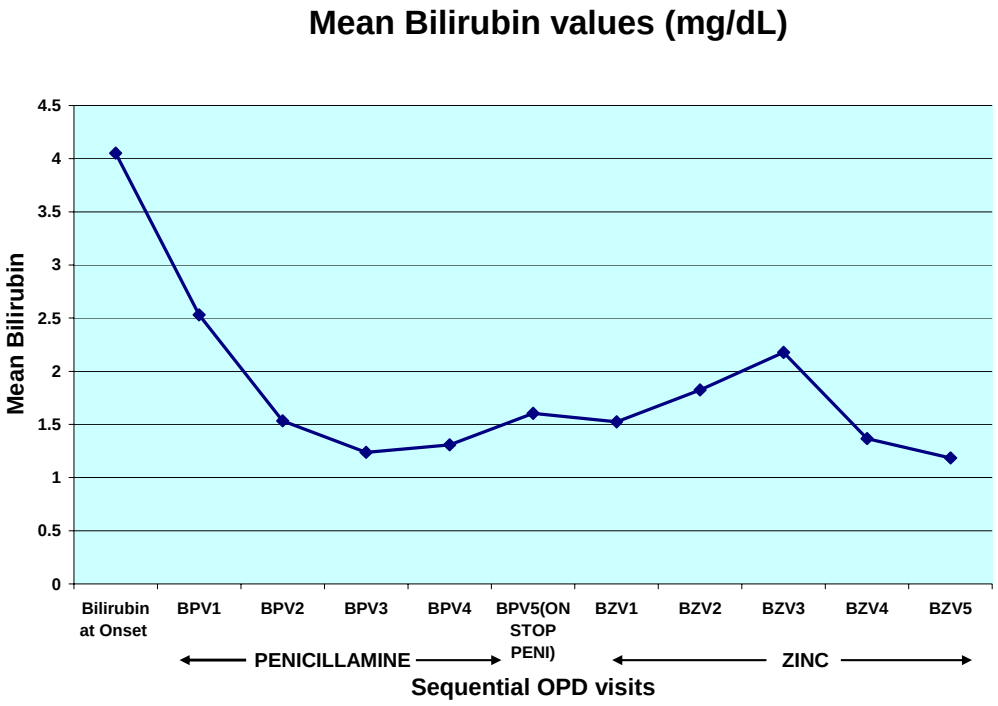


Figure 7 - Figure to show the mean bilirubin values on sequential follow up

The mean serum albumin values at presentation, on penicillamine and on zinc were 2.73 mg%, 3.49 mg% and 3.95 mg% respectively. The variation among the means between the various groups was highly significant on ANOVA testing (p= 0.0001). There was statistically significant difference on comparing the mean serum albumin at presentation with both penicillamine treatment (p<0.01) and zinc monothearpy (p<0.01). However, no significant difference was found when penicillamine and zinc were compared (p>0.05).

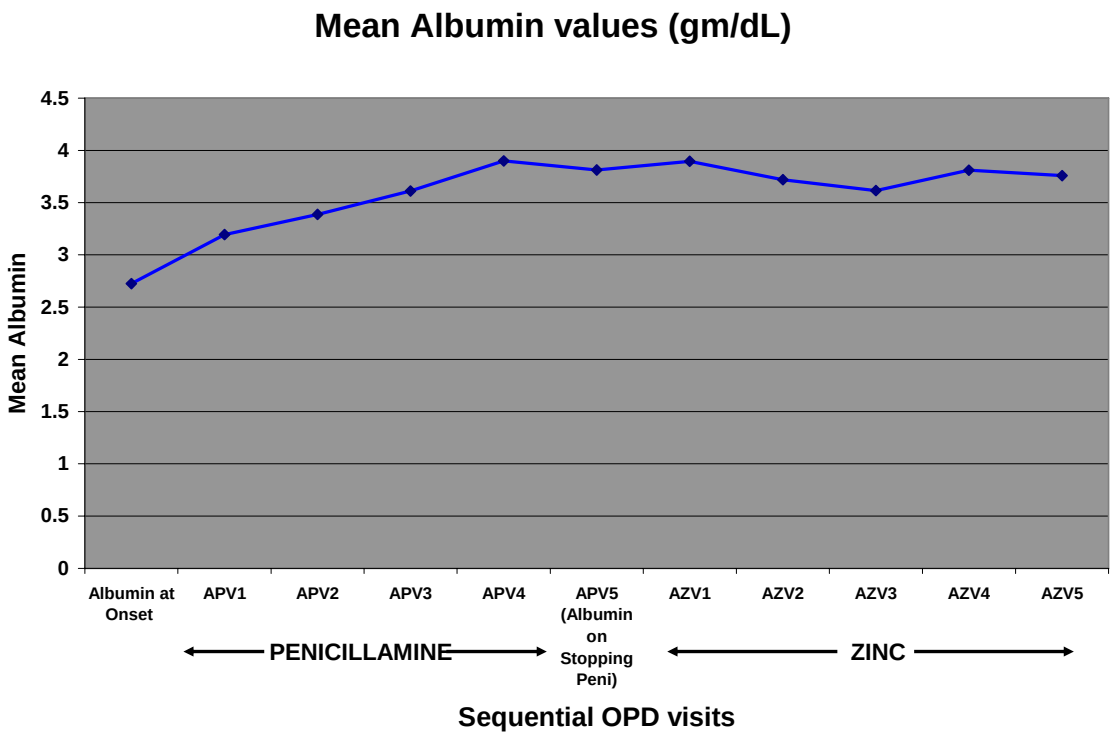


Figure 8 - Figure to show the mean albumin values on sequential follow up

The mean hemoglobin values at presentation, on penicillamine and on zinc were 10.26 gm%, 11.49 gm% and 11.83 gm% respectively. There was no statistically significant differences in the mean hemoglobin values on penicillamine and on zinc ($p>0.05$). There was statistically significant difference on comparing mean hemoglobin values at presentation versus penicillamine ($p<0.05$) and zinc ($p<0.05$).

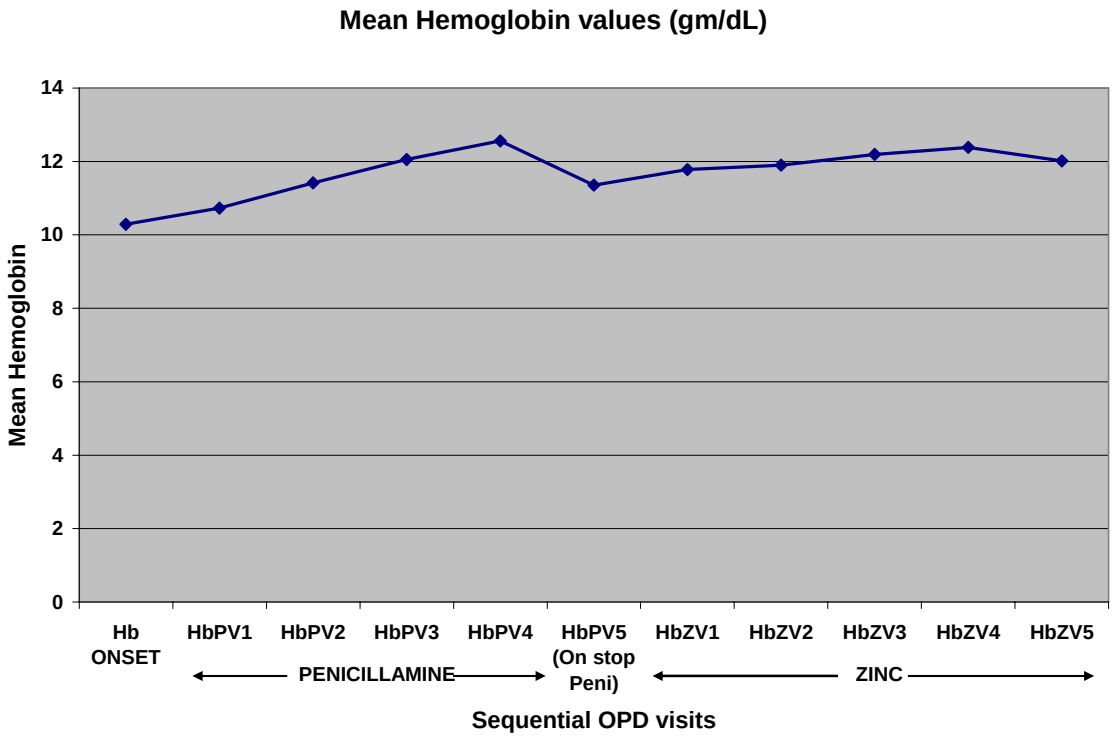


Figure 9 – Figure to show the mean hemoglobin values on follow up

The mean total count at presentation, on penicillamine and on zinc were 7144 cells/cmm, 5339 cells/cmm and 4913 cells/cmm respectively. There was significant difference between mean total counts at presentation versus zinc ($p<0.05$). In contrast, there was no statistically significant difference between the mean total count at presentation vs that on penicillamine treatment ($p>0.05$) and on penicillamine vs zinc ($p>0.05$).

The mean platelet count at presentation, on penicillamine and on zinc were 1,29,290 cells/cmm, 1,10,955 cells/cmm and 1,07,683 cells/cmm. There was no statistically significant difference in the mean platelet count at presentation, on penicillamine and on zinc ($p>0.05$).

The mean prothrombin time at presentation, on penicillamine and on zinc were 20.8 seconds, 15.9 seconds and 14.6 seconds respectively. The variation among the means between the various groups was highly significant ($p= 0.0004$). There were statistically significant differences when the prothrombin time at presentation was compared with that on penicillamine ($p<0.01$) and zinc ($p<0.001$). This was not the case when the mean prothrombin time on penicillamine and on zinc were compared ($p<0.05$).

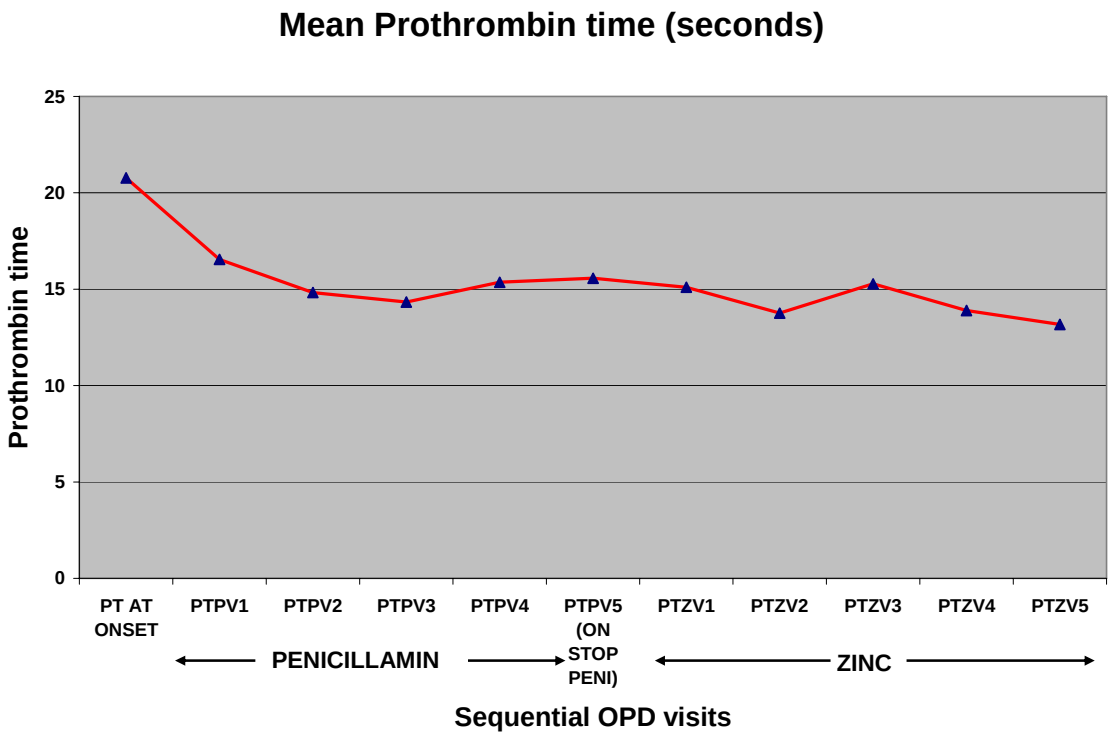


Figure 10 - Figure to show the mean prothombin time values on follow up

The mean 24 hour urinary copper values at presentation, on penicillamine and on zinc were 578.61 µg, 631.46 µg and 195.35 µg respectively. The variation among the means between the various groups was highly significant (p= 0.0004). There was a significant difference in the mean 24 hour urinary copper values on penicillamine vs zinc ($p<0.01$) as well as at presentation vs on zinc ($p<0.01$). However, values at presentation vs on penicillamine did not yield significant results ($p>0.05$).

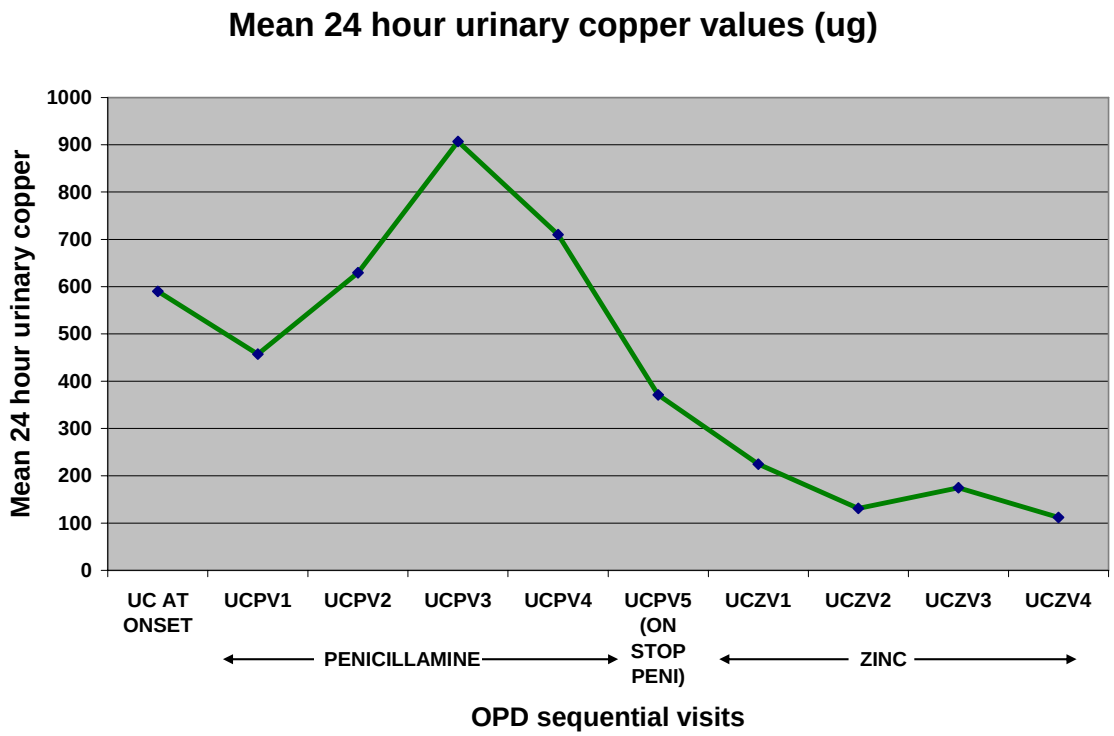


Figure 11 – Figure to show the mean 24 hour urinary copper on follow up

The mean Model for End Stage Liver Disease (MELD) scores at presentation, on penicillamine and on zinc were 11.71, 4.5 and 5.4 respectively. The variation among the means between the various groups was highly significant (p= 0.0002). There was a statistically significant difference in the MELD score at presentation vs both on penicillamine and on zinc ($p<0.001$ and $p<0.01$ respectively). This significant difference was not observed when the MELD scores on penicillamine and zinc were compared ($p>0.05$).

The mean Nazer scores at presentation, on penicillamine and on zinc were 3.09, 0.57 and 0.59 respectively. The variation among the means between the various groups was highly significant on ANOVA testing (p= 0.0001). There was a statistically significant difference in the Nazer score at presentation vs both penicillamine (p<0.01) and zinc (p<0.01). The mean Nazer score showed no significant difference on penicillamine vs zinc (p>0.05).

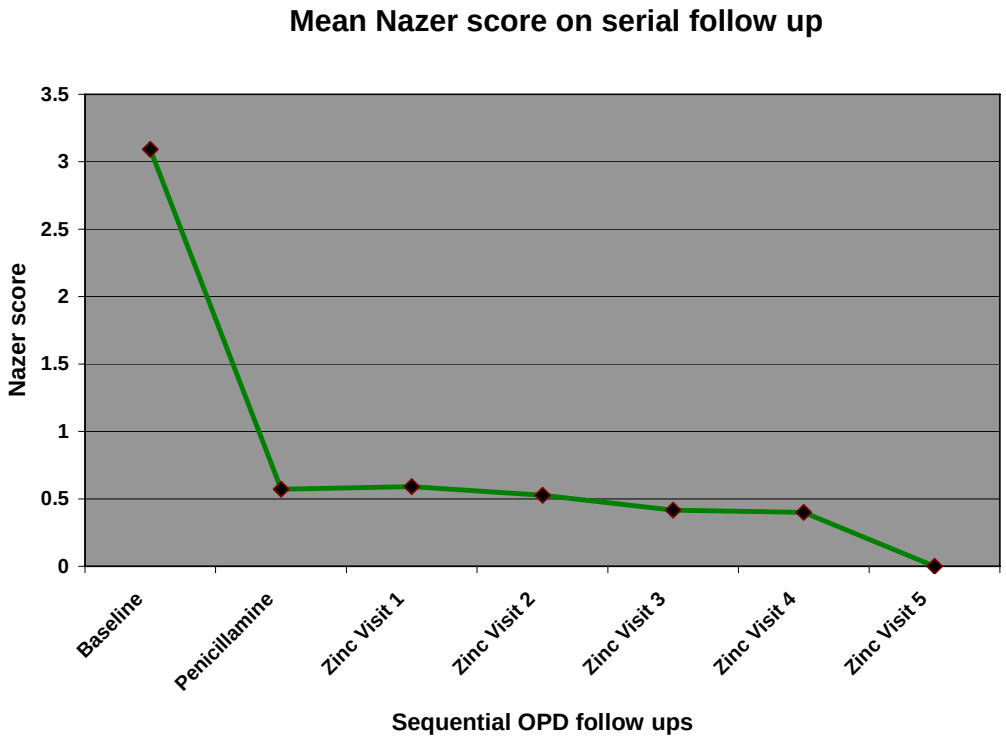


Figure 12 – Figure to show the mean Nazer score on sequential follow up

The mean New Wilson Index for Predicting Mortality at presentation, on penicillamine and on zinc was 6.31, 2.26 and 2.19 respectively. The variation among the means

between the various groups was highly significant (p= 0.0001). There was statistically significant differences in the mean index when baseline values were compared with penicillamine (p<0.001) as well as zinc (p<0.001). When the comparison was made between penicillamine and zinc the difference was not statistically significant (p>0.05).

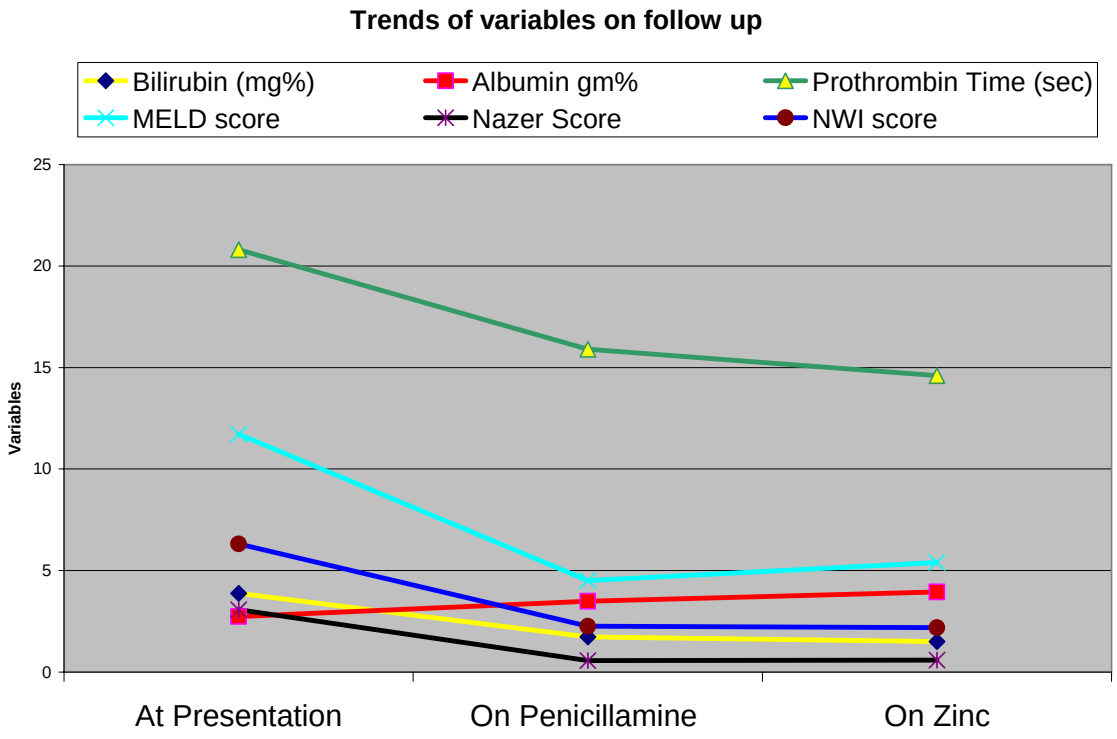


Figure 13 – Figure to show the trend of various biochemical and hematological parameters and clinical scores at baseline and on therapy

	Mean Values			P value		
Variable	**Baseline**	**Penicillamine**	**Zinc**	**Baseline vs Penicillamine**	**Baseline vs Zinc**	**Penicillamine vs Zinc**
Bilirubin	3.88	1.73	1.51	>0.05	>0.05	>0.05
Albumin	2.73	3.49	3.95	**<0.01**	**<0.01**	>0.05
PT	20.8	15.9	14.6	**<0.01**	**<0.001**	>0.05
MELD	11.71	4.5	5.4	**<0.001**	**<0.01**	>0.05
Nazer score	3.07	0.57	0.59	**<0.01**	**<0.01**	>0.05
NWI	6.31	2.26	2.19	**<0.001**	**<0.001**	>0.05

Table 1 - Table to show the mean values of the variables and comparison of p values amongst different groups

The dose of penicillamine varied from 250 mg twice a day to 250 mg four times per day. Patients were given 20 mg of pyridoxine along with penicillamine. The dose of zinc sulfate varied from 140 mg twice a day to 140 mg thrice a day.

3 patients were lost to follow up after starting zinc monotherapy. All patients except one who had recently begun treatment with zinc had at least one visit post initiation of zinc treatment.

Adverse effects and Complications on treatment:

Patients on penicillamine had severe life threatening side effects which included neutropenia (n=3), thrombocytopenia (n=1), anemia (n=1) and proteinuria (n=1). In stark contrast, adverse effects noted with zinc were minimal. Only one patient complained of dyspepsia while on zinc therapy which subsided with empirical treatment.

Complications noted with penicillamine therapy were more severe as well as more common than those with zinc. The frequent complications noted in patients on penicillamine were spontaneous bacterial peritonitis (n=4) {after 2 weeks, 4 weeks, 1 month and 3 months of penicillamine respectively}; variceal bleed (n=3) {2 months, 9 months and 2 years of penicillamine respectively}; and portal colopathy related rectal bleeding (n=1) {2 months of penicillamine}. Other features noted were speech disturbances and poor scholastic performance in one patient and serositis causing pleural effusion in another.

Three patients had variceal bleed while on zinc. They developed variceal bleed after 9 months, 17 months and 20 months respectively of treatment with zinc. Two of these patients had had an earlier variceal bleed while on penicillamine. There were no other complications of liver disease while on zinc. Drooling of saliva and behavioral changes were noted in one patient 5 years after being initiated on zinc treatment.

Follow up:

There was one death on follow up. This patient, who had presented with hepatic decompensation continued to be in a decompensated state while on treatment and later succumbed to septic complications. This happened 57 weeks of zinc treatment which was initiated after 14 weeks of penicillamine.

The compliance with zinc was 100%. One patient stopped penicillamine for 2 weeks, reasons for which are not known.

Out of the 28 patients, 24 were decompensated at presentation. Three patients, who had initially presented with decompensation, were lost to follow up after being initiated on zinc. 18 patients became compensated while on zinc after an initial period of penicillamine.

Two patients had a Nazer score ≥ 7 at baseline which is an indicator of higher chances of mortality without liver transplantation. Both these patients were managed successfully with penicillamine followed by zinc. Both these patients are still surviving on zinc monotherapy.

Discussion

Ours is a partly retrospective and partly prospective observational cohort study. This research project primarily studied symptomatic patients of WD with hepatic (+/- neurological/psychiatric) manifestations. The patients were initiated on decoppering therapy with penicillamine but were unable to continue it due to financial constraints or development of adverse effects. The patients were subsequently initiated on zinc monotherapy.

This is the largest series of patients with symptomatic hepatic Wilson's disease. There is an adequate duration of follow up after initiating patients on zinc with a mean follow up of 3 years 4 months. Earlier studies with zinc monotherapy having large sample size include patients in presymptomatic stage [67] or with neurological WD [49,78].

The American Association for the Study of Liver Diseases does not at present recommend the use of zinc in patients with symptomatic hepatic WD [8]. Zinc has been used from the start as monotherapy in the series by Linn et al. [70] and Hoogenraad et al. [79], which included symptomatic neurological and hepatic WD patients. The study by Brewer et al. [41] uses zinc as the sole maintenance therapy after patients were initially treated with chelating agents. Earlier studies include case reports of patients who were treated with zinc only when patients had adverse effects to penicillamine or there was deterioration of neurological symptoms [52]. There are few case reports of the successful use of zinc monotherapy in patients presenting primarily with hepatic symptoms [80,81,82].

Our study shows a favourable trend of hematological (hemoglobin, prothrombin time) and biochemical parameters (serum albumin) on penicillamine as compared to baseline which was statistically significant. This positive trend in the parameters persists after switching over to zinc therapy.

There was no statistical difference in the means of biochemical parameters between penicillamine and zinc monotherapy. Serum bilirubin values also improve on therapy but the trend was not statistically significant.

The improvement in the MELD score [83], Nazer score [72] and New Wilson disease index for predicting mortality [84] between baseline and penicillamine therapy persists on zinc therapy which is of marked clinical significance.

The 24 hour urinary copper values shows a significant rise on penicillamine therapy which is not seen on zinc therapy ($p<0.01$) which reiterates the fact that zinc primarily acts by preventing copper absorption from the gastrointestinal tract where as penicillamine acts by chelation of body copper stores and hence the high levels of copper in urine on penicillamine therapy.

Four decompensated patients received penicillamine for less than six months (2, 8, 12 and 14 weeks respectively). 3/24 decompensated patients were lost to follow up. One decompensated patient who was changed over to zinc at 14 weeks of penicillamine

monotherapy due to anemia remained decompensated on zinc therapy and died due to gram negative sepsis after 57 weeks of zinc therapy.

The side effect profile was similar as documented earlier in literature [7,8]. Patients on penicillamine had severe life threatening haematological side effects which included neutropenia, thrombocytopenia, anemia as well as proteinuria. In stark contrast, adverse effects noted with zinc were minimal and amenable to therapy.

Overall compliance was good with both the drugs except for one patient stopping penicillamine therapy for 2 weeks, details of which were not available. No patient stopped zinc.

The study by Linn et al [70] used zinc monotherapy from the diagnosis for symptomatic neurological and hepatic WD. Although the outcome for neurological WD was good, a few (2/12) patients with hepatic WD deteriorated on therapy with an unfavorable outcome. In contrast the study by Sinha et al. [78] that studied patients of neurological WD, there was a mean duration of initial combination therapy with penicillamine and zinc for 107.4 months before shifting over to zinc monotherapy. The patients in the study groups showed a statistically significant improvement in their neurological scores on zinc therapy after initial combination therapy. In our study, 24/28 subjects had a minimum period of six months of decoppering with penicillamine before switching over to zinc (4 patients were changed over to zinc earlier due to severe adverse effects to penicillamine).

The very fact that all decompensated patients who received adequate initial chelation with penicillamine became compensated continue to be so on zinc monotherapy with negligible side effects implies that zinc is an ideal agent for maintenance therapy after initial chelation in hepatic WD.

The major limitation of our study was that it was partly retrospective.

At present there is no prospective data to find out the exact duration of penicillamine chelation therapy required to stabilize a patient. A prospective trial with varying durations of initial chelation therapy with penicillamine followed by zinc monotherapy will be of utmost importance. However the duration of penicillamine therapy shall always be guided by the clinical and laboratory parameters in an individual patient. A prospective head to head trial between patients on exclusive penicillamine and those on penicilliamine/zinc sequential therapy would be beneficial.

Conclusions

1. Penicillamine is a good drug for initial chelation therapy for patients with symptomatic Wilson's disease.

2. Penicillamine has serious and life threatening adverse effects.

3. Zinc can be used as a monotherapy for symptomatic patients of WD, provided patients are adequately chelated and stabilized on penicillamine initially.

4. Zinc has minimal and tolerable non life threatening adverse effects.

5. Initial chelation with penicillamine followed by maintenance zinc monotherapy is an efficacious regime to treat symptomatic patients of hepatic Wilson's disease.

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Proforma

Patient Study Number: Date of 1st presentation to CMC:

Name: Date of Birth:

Age: Sex: Consanguineous Marriage: Y / N

Fathers Name: Name of Mother:

Siblings

Name	Date of Birth / Age	Affected

Postal Address:

Phone No: a) b)

Email:

Diagnostic Criteria for Wilsons Disease:

Mode of Presentation:

Mode	Features	Age of onset of symptoms	Details
Hepatic	Symptomatic		
	Asymptomatic		
Neurological	Symptomatic		
	Asymptomatic		
Psychiatric			
Others			

Kay-Fleischer Ring: Present / Absent

Penicillamine therapy profile

Date	Weight	Dose	Compliance (Y/N)

Date of Onset:

Date stopped:

Duration taken:

Date							
Hb							
TC							
DC							
Platelet							
PT							
INR							
T. Prot							
Albumin							
T. Bili							
D. Bili							
AST							
ALT							
ALP							
Creatinine							
Serum Ceruloplasmin							
24 hr urinary copper							

Complications of Liver Disease on Penicillamine therapy

	Dates	Details	Duration of Penicillamine therapy
Variceal bleed			
Ascites			
Hepatic enceph			
Any other			

Details of worsening of disease on treatment:

Exact duration of treatment stopped when on penicillamine and reason:

Side effects attributable to Penicillamine treatment

Side effects	Dates	Details	Duration of Penicillamine therapy

Zinc therapy profile: Zinc sulphate / Zinc acetate

Date	Weight	Dose	Compliance (Y/N)

Date of Onset:

Date stopped:

Duration taken:

Date							
Hb							
TC							
DC							
Platelet							
PT							
INR							
T. Prot							
Albumin							
T. Bili							
D. Bili							
AST							
ALT							
ALP							
Creatinine							
Serum Ceruloplasmin							
24 hr urinary copper							

Complications of Liver Disease during Zinc Monotherapy

	Dates	Details	Duration of Zinc therapy
Variceal bleed			
Ascites			
Hepatic enceph			
Any other			

Details of worsening of disease on treatment:

Exact duration of treatment stopped when on zinc and reason:

Side effects attributable to Zinc treatment

Side effects	Dates	Details	Duration of Zinc therapy

Exact details how Penicillamine changed to zinc:

	At presentation	On stopping penicillamine	On zinc monotherapy
Nazer Score			
New WD PI			
CPT score			
MELD score			

USG Abdomen Date:

Report:

OGD Date:

Report:

Follow Up Remarks:

Date	Remarks/Quality of life

Iron indices on treatment:

Death if any details:

Abstract

TITLE OF THE ABSTRACT : EFFICACY OF INITIAL CHELATION WITH PENICILLAMINE FOLLOWED BY ZINC MONOTHERAPY IN SYMPTOMATIC WILSON'S DISEASE

DEPARMENT : CLINICAL GASTROENTEROLOGY AND HEPATOLOGY

NAME OF THE CANDIDATE : MEHUL CHOKSI

DEGREE AND SUBJECT : DM GASTROENTEROLOGY

NAME OF THE GUIDE : C E EAPEN. MD, DM.
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OBJECTIVES:

There are no recommendations for use of zinc in symptomatic Wilson's disease (WD). The aim was to study the clinical outcome of patients with symptomatic WD who were changed from penicillamine to zinc due to financial constraints or adverse effects.

METHODS:

All patients of patients of symptomatic hepatic +/- neurological/psychiatric manifestations of WD changed over from penicillamine to zinc sulfate and formed the study cohort. Diagnosis other than WD, atypical copper deposition disease and

presymptomatic WD were excluded. Clinical and laboratory details at presentation, on penicillamine and on zinc were recorded. At each follow up visit and clinical worsening or improvement, compliance and adverse effects were recorded. The patients had periodic monitoring of hemoglobin, TC/DC, platelet count, liver function tests and prothrombin time. MELD and Nazer score and NWI were calculated at presentation, on penicillamine and on zinc. ANOVA was the statistical test used for comparing the means of variables at baseline, on penicillamine and on zinc therapy.

RESULTS:

28 patients formed the study cohort. 26 with pure hepatic manifestation, 2 with added neurological and 2 with added psychiatric manifestations. The mean age of subjects was 17.5 ± 6.19 years. Mean duration of penicillamine therapy was 123.92 weeks (SD: 94.18; range: 2-320 weeks). The mean duration of zinc therapy was 175.92 weeks (SD: 122.82; range: 21 to 352 weeks). On follow up there was serial improvement in the serum bilirubin, serum albumin, PT INR, MELD score, Nazer score and Wilson disease prognostic index. Penicillamine is a good drug for initial chelation therapy for patients with symptomatic WD. Once switched over to zinc monotherapy these patients continue to remain compensated with maintenance or improvement of laboratory parameters and/or clinical scores. Penicillamine has serious and life threatening side effects where as zinc has minimal, tolerable and non life threatening side effects. Initial chelation with penicillamine followed by maintenance zinc monotherapy is an efficacious regime to treat symptomatic patients of hepatic Wilson’s disease.